

Food and Drug Administration Silver Spring, MD 20993

Mark Klinger Associate Director, Regulatory Affairs Endo Pharmaceuticals Inc. 100 Endo Boulevard Chadds Ford, PA 19317

**RE:** NDA #021732

VANTAS® (histrelin acetate) subcutaneous implant

MA #123

Dear Mr. Klinger:

The Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP) of the U.S. Food and Drug Administration (FDA) has reviewed a Caregiver Brochure (VN-01094b) (brochure) for VANTAS® (histrelin acetate) subcutaneous implant (Vantas) submitted by Endo Pharmaceuticals Inc. (Endo) under cover of Form FDA-2253. The brochure is misleading because it omits serious risk information for Vantas. Thus, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) and 321(n). 21 CFR 1.21.

## **Background**

Below is the indication and summary of the most serious and most common risks associated with the use of Vantas.<sup>1</sup>

According to the FDA-approved product labeling (PI), Vantas is indicated for the palliative treatment of advanced prostate cancer.

Vantas is associated with several serious risks. According to the PI, Vantas is contraindicated in patients with hypersensitivity to gonadotropin releasing hormone (GnRH), GnRH agonist analogs, or any of the components in the drug since anaphylactic reactions to synthetic GnRH agonist analogs have been reported in the literature. Vantas is also contraindicated in women who are or who may become pregnant, as it can cause fetal harm.

Vantas has warnings and precautions regarding the onset of new or worsening symptoms due to a transient increase in serum concentrations of testosterone during the first week of treatment; spinal cord compression (which may result in paralysis) and ureteral obstruction

Reference ID: 3194707

<sup>&</sup>lt;sup>1</sup> This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

(which may cause renal impairment); difficulty in locating or removing the implant; hyperglycemia and increased risk of developing diabetes mellitus; increased risk of developing myocardial infarction, sudden cardiac death, and stroke; and periodic monitoring of serum concentrations of testosterone and prostate-specific antigen to assess response to the drug.

The most common adverse reactions that occurred with Vantas therapy in >5% of men were hot flashes, fatigue, implant site reaction, and testicular atrophy.

## **Omission of Risk Information**

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The brochure contains several claims discussing the efficacy and dosing regimen benefits of Vantas. For example,

- "One kind of ADT [androgen deprivation therapy] is a gonadotropin releasing hormone (GnRH) agonist, which works by decreasing the amount of testosterone that the body makes. This decrease in testosterone can slow the growth of prostate cancer cells.
  - "VANTAS® is one type of GnRH agonist that may help relieve the symptoms of prostate cancer; it is not a cure. It is implanted into the arm and is designed to continuously deliver drug every day for 12 months. Because of its once-yearly administration, VANTAS may mean fewer interruptions to your loved one's life, and possibly yours." (page six)
- "VANTAS® (histrelin acetate) subcutaneous implant is a once-yearly hormone suppression therapy for prostate cancer. Hormone therapies like VANTAS may help relieve the symptoms of advanced prostate cancer, but are not a cure. VANTAS is different from multiple injection therapies because with one implant per year, your loved one continuously receives 12 months of medicine. This may mean less interruptions to his life and less time spent at doctor appointments specifically for the administration of a GnRH agonist. Fewer treatment administrations may mean less time in a doctor's office for you too." (page 10)

However, the brochure fails to state that paralysis may result from the risk of spinal cord compression, and that patients are at increased risk of developing hyperglycemia, diabetes mellitus, myocardial infarction, sudden cardiac death, and stroke. As a result, the brochure misleadingly suggests that Vantas is safer than has been demonstrated.

## **Conclusion and Requested Action**

For the reasons described above, the brochure misbrands Vantas in violation of the FD&C Act, 21 U.S.C. 352(a) and 321(n). 21 CFR 1.21.

OPDP requests that Endo immediately cease the dissemination of violative promotional materials for Vantas such as those described above. Please submit a written response to this letter on or before October 10, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Vantas that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266 or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to OPDP. OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP), and DCDP. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #123 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Vantas comply with each applicable requirement of the FD&C Act.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C Regulatory Review Officer Division of Consumer Drug Promotion Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, PharmD, CPA
Team Leader
Division of Consumer Drug Promotion
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/s/

MICHELLE L SAFARIK
09/25/2012

AMY TOSCANO